



NDA #####

**SAFETY LABELING CHANGE NOTIFICATION**

COMPANY NAME  
STREET  
CITY, STATE ZIP CODE  
Attention: COMPANY CONTACT

Dear COMPANY CONTACT:

Please refer to your New Drug Applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for [TRADENAME].

**SAFETY LABELING CHANGE**

Section 505(o)(4) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to make safety related label changes based upon new safety information that becomes available after approval of the drug or biological product.

Since [TRADENAME] was approved on [date of approval], we have become aware of a serious risk of disabling and potentially irreversible adverse reactions with the class of systemic fluoroquinolone antibacterial drug products, of which [TRADENAME] is a member. These serious adverse reactions have been observed to occur together, and include tendinitis, tendon rupture, peripheral neuropathy, and central nervous system effects. This information is based on our review of postmarketing adverse event reports from the FDA Adverse Event Reporting System (FAERS). This safety information was discussed at a November 5, 2015 joint meeting of the Antimicrobial Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. The committee members recommended labeling changes to describe the new safety information and to limit the use of systemic fluoroquinolone antibacterial drugs for the indications of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and uncomplicated urinary tract infections to patients who do not have other treatment options. We consider this information to be “new safety information” as defined in section 505-1(b)(3) of the FDCA.

In accordance with section 505(o)(4) of the FDCA, we are notifying you that based on the new safety information described above we believe that the new safety information should be included in the labeling for the systemic fluoroquinolone antibacterial drugs, including [TRADENAME], as described below.

The required labeling changes reflect the inclusion of the new safety information that serious adverse reactions can occur together and can be disabling and potentially irreversible. As a result of the new safety information, the benefits of antibacterial drugs were evaluated for

the indications of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and uncomplicated urinary tract infections. Because these infections can be self-limiting in some patients, the risks of serious adverse reactions, which also include the risks based on the new safety information, outweigh the benefits for patients who have other treatment options. The required labeling changes reflect a new limitation of use statement to make it clear that the use of [TRADENAME] for these indications are to be reserved for patients who do not have other treatment options.

The following list summarizes the required safety labeling changes and does not reflect the full text of product labeling.

## **PRESCRIBING INFORMATION**

### **HIGHLIGHTS**

- **BOXED WARNING**

Revise the BOXED WARNING to include the new safety information of serious adverse reactions including tendinitis, tendon rupture, peripheral neuropathy, and central nervous system effects. To minimize the risk, the BOXED WARNING must include the statement to reserve [TRADENAME] for use in patients who have no alternative treatment options for acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and uncomplicated urinary tract infections.

- **INDICATIONS AND USAGE**

Revise the INDICATIONS AND USAGE section to list the serious and potentially life-threatening infections first, followed by acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and uncomplicated urinary tract infections.

### **FULL PRESCRIBING INFORMATION**

- **BOXED WARNING**

Same changes as the Boxed Warning in Highlights above.

- **INDICATIONS AND USAGE**

The INDICATIONS AND USAGE must contain a limitation of use statement for acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and uncomplicated urinary tract infections to reserve [TRADENAME] for treatment in patients who have no alternative treatment options. In addition, include the same changes as in Highlights above.

- **DOSAGE AND ADMINISTRATION**

Rearrange the DOSAGE AND ADMINISTRATION tables to list the serious infections first, followed by acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and uncomplicated urinary tract infections.

- **WARNINGS AND PRECAUTIONS**

The WARNINGS AND PRECAUTIONS must contain the new safety information on disabling and potentially irreversible serious adverse reactions as a new subsection heading at the beginning of this section. Rearrange the order of the WARNINGS AND PRECAUTIONS in accordance with the Boxed Warning. Revise the descriptions of Tendinitis and Tendon Rupture, Peripheral Neuropathy, and Central Nervous System Effects. Revise Other Serious and Sometimes Fatal Adverse Reactions to appear in order before Hypersensitivity Reactions.

- **PATIENT COUNSELING INFORMATION**

The patient counseling information must include the new safety information with regards to disabling and potentially irreversible serious adverse reactions. Revise the patient counseling information to describe the adverse reactions first.

## **PATIENT LABELING**

- **MEDICATION GUIDE**

The Medication Guide must include the new safety information.

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a rebuttal statement detailing the reasons why such a change is not warranted. If you submit a supplement that includes only language identical to that specified in the attached label, the supplement may be submitted as a changes being effected (CBE-0) supplement. If the supplement includes proposed language that differs from that in the attached label, submit a prior approval supplement (PAS).

We have determined that an extension of the discussion period will be warranted to allow us to complete our review and reach agreement on the content of the labeling. Therefore, the discussion period for your supplement or rebuttal statement will begin when the submission is received, and end by August 10, 2016, unless additional discussion extensions are warranted.

Requirements under section 505(o)(4) apply to NDAs, BLAs, and ANDAs without a currently marketed reference listed drug approved under an NDA, including discontinued products, unless approval of an application has been withdrawn in the Federal Register. Therefore, the requirements described in this letter apply to you, unless approval of your application has been withdrawn in the Federal Register.

Under section 502(z), failure to submit a response in 30 days may subject you to enforcement action, including civil money penalties under section 303(f)(4)(A) and an order to make whatever labeling changes FDA deems appropriate to address the new safety information.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

**SAFETY LABELING CHANGES UNDER 505(o)(4) – CHANGES BEING EFFECTED**

**OR**

**SAFETY LABELING CHANGES UNDER 505(o)(4) - PRIOR APPROVAL SUPPLEMENT**

**OR**

**SAFETY LABELING CHANGES UNDER 505(o)(4) – REBUTTAL (CHANGE NOT WARRANTED).”**

Prominently identify subsequent submissions related to the safety labeling changes supplement with the following wording in bold capital letters at the top of the first page of the submission:

**SUPPLEMENT <<insert assigned #>>**

**SAFETY LABELING CHANGES UNDER 505(o)(4) - AMENDMENT**

If you do not submit electronically, please send 5 copies of the submission.

**OTHER LABEL CHANGES**

In addition, editorial changes are provided to the package insert so as to furnish adequate information for the safe and effective use of this product. These changes are not required under section 505(o)(4).

If you have any questions, call Susmita Samanta, Safety Regulatory Project Manager, at (301) 796-0803.

Sincerely,

*{See appended electronic signature page}*

Joseph G. Toerner, M.D., M.P.H.  
Deputy Director for Safety  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research